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Endocannabinoids Mediate Synaptic Plasticity at Mixed Synapses

Jozsef Vigh[1] and Henrique von Gersdorff[2,*]
[1]Department of Biomedical Sciences, Colorado State University, Ft. Collins, CO 80523, USA
[2]Vollum Institute, Oregon Health & Science University, Portland, OR 97239, USA
*Correspondence: vongersd@ohsu.edu
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Endocannabinoids are generally known to suppress excitatory or inhibitory synaptic transmission. Now, in an elegant series of experiments, Cachope et al. reveal a novel signaling pathway whereby endocannabinoids indirectly potentiate mixed chemical and electrical synapses. Gap junction-mediated transmission can thus be potentiated via distinct frequency-dependent mechanisms.

Rapid signaling in the nervous system is accomplished most commonly by chemical synapses, where a neurotransmitter released by the presynaptic terminal alters ionic flow through the postsynaptic membrane. Even faster signal transfer can be achieved if two neurons are directly connected via gap junctions: highly specialized channels through which electrical currents flow from one cell to another. Multiple neuromodulatory mechanisms have been shown to alter gap junctional coupling between neurons. In spite of this, electrical synapses are still mainly perceived as passive intercellular channels with limited modifiability. This perception stems from a relative paucity of data about activity-dependent plasticity at electrical synapses, whereas activity-dependent plasticity has been well studied at chemical synapses. However, a fascinating new study by Cachope et al. (2007) in the current issue of *Neuron* sheds more light on this aspect of gap junctional communication. It indicates that electrical synapses can be just as complex and rich in modulatory signals as chemical synapses.

Cachope et al. (2007) investigated the synapse formed by the Club endings of the auditory nerve on the lateral dendrite of the goldfish Mauthner cell (M cell), which has a long and distinguished history in electrical synapse research due to its accessibility for both physiological and ultrastructural characterization (Furshpan, 1964). This is a mixed synapse where glutamatergic synapses work in parallel with gap junctions formed by connexin 35 (Cx35, the fish ortholog of the mammalian neuronal gap junction protein Cx36; O'Brien et al., 1998). This synapse provided the first evidence for activity-dependent NMDA receptor-mediated, LTP-like enhancement of electrical transmission in response to tetanic stimulation of the Club endings (Yang et al., 1990). The new findings demonstrate that yet another plasticity mechanism is present at this synapse, depending on the activity patterns of the Club endings (Figure 1). Whereas short trains of high-frequency stimulations of the auditory nerve (brief bursts of 10 ms pulses at 500 Hz, over several minutes) potentiated both the chemical and electric transmission via NMDA receptor activation (Yang et al., 1990) followed by Ca^{2+}/calmodulin-dependent kinase II action (Pereda et al., 1998), a lower-frequency stimulation (five pulses for 1 s at 100 Hz) enhanced the mixed EPSPs evoked by Club endings in the M cells via an endocannabinoid mechanism (Cachope et al., 2007). This is a remarkable finding because endocannabinoids have up to now been shown to mostly inhibit transmitter release, not potentiate it (Diana and Marty, 2004; Kushmerick et al., 2004).

The pathway by which the endocannabinoids triggered enhancement of the Club ending evoked mixed EPSPs in M cells is surprisingly elaborate: dendritic depolarization paired with mGluR1 receptor activation triggered endocannabinoid (presumably 2-arachidonyl-glycerol, 2-AG) release from the M cell. The 2-AG activated nearby CB1 receptors located on dopaminergic varicosities, which in turn evoked the release of dopamine, perhaps by modulating presynaptic potassium channels or via alternative, nonconventional intracellular signaling pathways. The dopamine then via D1/5 receptors activated PKA in M cells to phosphorylate Cx35 and glutamate receptors at the Club endings to enhance both glutamate-gated and the gap junctional conductance (Figure 1).

M cells are a pair of uncommonly large reticulospinal neurons participating in the fish tail-flick escape response (Eaton et al., 2001). Initiation and directional characteristics of this escape response depend on coded information from the otolith organs carried by the auditory nerve. In the goldfish, saccular afferents are most sensitive to sound pressure in the frequency range from 200 to 800 Hz. This is sensed by the abdominal swimbladder and projected to both sacculi via the Weberian ossicles in a probably highly correlated nondirectional manner (Fay, 1995). Remarkably, in goldfish, an intact swimbladder is required for M cell response (Eaton et al., 2001). Primary afferents of the saccule, lagena, and utricle of the goldfish also respond with greater sensitivity to acoustic particle motion between 100 and 200 Hz. This later input arises from the acceleration of the fish in a sound field and is inherently directional (Fay, 1995). Based on the striking match between the stimulations evoking synaptic enhancement and

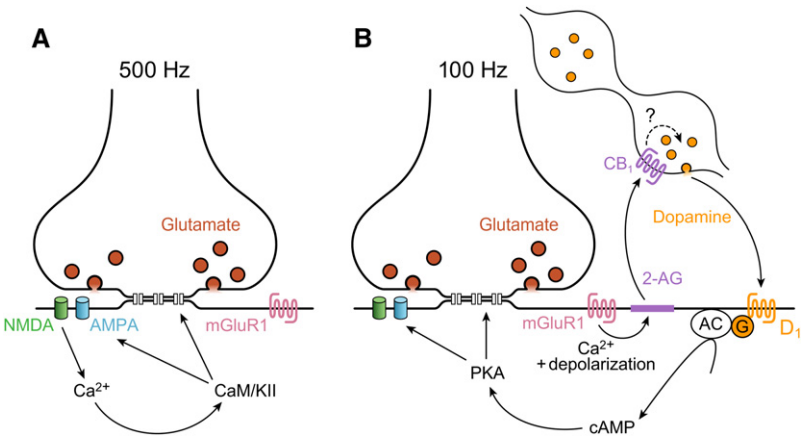

Figure 1. Frequency-Dependent Potentiation of the Club Ending-Mauthner Cell Mixed Electrical-Chemical Synapse

(A) High-frequency (500 Hz), tetanic stimulation of auditory nerve fibers evokes classic LTP-like potentiation of both the electrical and chemical component of the EPSP. Ca^{2+} influx through NMDA receptors activates calmodulin-dependent protein kinase II (CaM/KII), which in turn targets both gap junctions and glutamate receptors to increase their conductance.

(B) Lower-frequency (100 Hz) stimulation triggers postsynaptic mGluR1 activation, which in turn together with dendritic depolarization of the Mauthner cell leads to endocannabinoid (2-AG) release. The 2-AG acts on nearby dopaminergic varicosities possessing CB1 receptors and increases dopamine release. Dopamine receptor (D1) activation on the Mauthner cell increases adenylate-cyclase activity (AC) through G protein (G) activation. The resulting increase in cAMP activates protein kinase A (PKA), which targets both gap junctions and glutamate receptors to enhance their conductance.

natural frequencies, it is tempting to speculate that the two different frequency-dependent potentiation mechanisms of the mixed EPSPs evoked by the Club endings in the M cells serve separate physiological roles: a classic, NMDA-dependent LTP-like enhancement influences the sound intensity component of the escape behavior, whereas the mGluR1-endocannabinoid-dopamine-dependent enhancement influences the direction component. Potentiation may be a key mechanism to separate behaviorally relevant inputs to the M cell from the high spontaneous activity of the afferents from the otolith organs.

Whereas Cx35 seems to be the most prevalent isoform here, several other connexins are also involved in electrical coupling of neurons (Connors and Long, 2004). To date, the most comprehensive data describing the role of the electrical coupling regulation in a well-known physiological context probably comes from the retina (Lasater and Dowling, 1985; DeVries and Schwartz, 1989). For example, in the mammalian retina light adaptation uncouples Cx36 connected AII amacrine cells via a D1 receptor mechanism (Bloomfield and Volgyi, 2004). Interestingly, electrical synapses formed by Cx36 between the inhibitory neurons of rodent thalamic reticular nucleus were shown to undergo mGluR-mediated long-term depression (Landisman and Connors, 2005).

The distribution of Cx36 expression predicts that electrical synapses are ubiquitous in the brain (Condorelli et al., 2000) and probably involved in synchronized activity among several types of CNS interneurons (Christie et al., 2005). Therefore, the prospects of learning more about a large array of activity-dependent modulatory mechanisms at gap junctions are now wide open. And next time you throw a pebble in a stream and see a fish quickly scurry away, you will know that powerful mixed synapses are at work.

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